REMARKS

Claims 1-11, 21-23 and 84 were pending in the present application.

Applicants have canceled claims 6 and 8, without prejudice, as being drawn to non-elected subject matter and amended claim 1, 7, 9 and 11, without prejudice. Applicants reserve the right to pursue the deleted subject matter in one or more continuing applications.

Claims 1 and 11 has been amended to clarify that which Applicants regard as the invention. Specifically, claim 1 has been amended to recite that the heterologous adenovirus E4 region or portion thereof is derived from a subgroup C adenovirus and the replication-defective adenovirus is an adenovirus of subgroup D. Support for this amendment can be found in the specification, as published as U.S. Patent Application No. 2004/0106194, for example, at paragraphs [0059]-[0060] and originally filed claim 6. Claim 7 has been amended to correct claim dependency in view of the canceled claim. Claim 9 has been amended to recite specific subgroup D adenoviruses. Support for this amendment can be found in the specification, for example, at paragraphs [0059]. Claim 11 has been amended to recite that the E1-complementing cell line expresses E1 from serotype 5. Support for this amendment can be found in the specification, for example, at paragraph [0062].

No new matter has been added by these amendments.

After entry of the foregoing amendments, claims 1-5, 7, 9-11, 21-23 and 84 will be pending.

Applicants respectfully request entry of the foregoing amendments and consideration of the following remarks.

Claim Rejections – 35 U.S.C. § 112

Claim 11 was rejected under 35 U.S.C. 112, second paragraph as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. In particular, the Examiner alleges that use of the trademark PER.C6® in claim 11 renders the identification/description of the specific cell line indefinite.

Without admitting to the propriety of the rejection and in an effort to advance prosecution of the present application, Applicants have amended claim 11 to delete reference to the trademark PER.C6®. Accordingly, the rejection has been rendered moot.

Claim Rejections – 35 U.S.C. § 103

Claims 1-11, 21 and 84 were rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Mehtali (U.S. Patent No. 6,475,480), Falck-Pedersen (U.S. Patent No. 5,849,561) and Li (U.S. Patent No. 7,026,164). Applicants respectfully traverse.

The legal standard and cited references have previously been discussed in the Amendment and Response to Office Action filed on March 6, 2007 ("March 2007 Amendment").

The Examiner contends that Mehtali describes the "use of a polynucleotide encoding one or more ORF(s) of the E4 region of an adenovirus selected from ORF1, ORF2, ORF3, ORF4, ORF3/4, ORF6/7, ORF6 and ORF7 taken individually or in combination, to improve the expression and/or persistence of expression of a recombinant gene in a host cell or organism". See Mehtali, abstract. Mehtali further describes that it is possible to insert certain E4 ORFs from the same or other adenovirus backbones in an adenovirus vector. See id., col. 4, lines 35-38. Mehtali discloses that the adenoviral vector may be propagated in a complementation cell line, which supplies in *trans* the deleted/mutated viral functions. See id., col. 10, lines 5-7. Mehtali further describes that it is possible to test the effect of an E4 ORF by providing it in *cis* or *trans* to a E4 deleted vector carrying a transgene and determining its expression". See id., col. 3, lines 61-64.

Falck-Pedersen discloses a method of producing a replication-deficient adenovirus in which the virus is deficient in both E1 and E4 functions in a cell that provides in *trans* gene functions of the E1 and E4 regions of one or more adenoviruses not belonging to the same serogroup as the replication-deficient adenovirus. See Falck-Pedersen, abstract.

Li discloses the packaging cell line, PER.C6®.

The Examiner contends that the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made because (1) one would have been motivated to combine the teachings of Falck-Pedersen and Mehtali because the teachings both reveal an enhanced production of replication deficient adenovirus by either using distinct serotypes as taught by Falck-Pedersen or preventing impaired transgene expression as taught by Mehtali; and (2) there would have been a reasonable expectation of success given that the cell line and the underlying molecular biology techniques were commonly used in the art for the production of adenovirus.

Applicants wish to reiterate their arguments made in the March 2007 Amendment. Briefly, Applicants have argued that there is no motivation to combine the teachings of Falck-Pedersen and Mehtali because (1) Lusky teaches away from the present invention and (2) the desirability of the combination has not been shown.

In responding to Applicants' arguments, the Examiner contends that these arguments are not persuasive because of the enhancement disclosed by Mehtali and Falck-Pedersen in a replication-deficient adenovirus would lead one to combine the teachings to obtain optimal results.

Applicants respectfully submit that the Examiner has not provided any reasoning why Lusky does not teach away from the invention and has not provided a reasoning why, in view of Lusky, the combination of Mehtali and Falck-Pedersen is desirable. As previously noted in the March 2007 Amendment, Lusky teaches that multiply deleted adenovirus vectors have clear advantages over E1 only deleted vectors, including (1) prevention of replication-competent adenovirus through recombination events, and (2) an improved safety profile due to the oncogenic potential of the E4 ORF6. See Lusky, pg. 2031, col. 1, last paragraph. Given this teaching, there would be a strong motivation to use the teachings of Falck-Pedersen (producing a virus using a cell line providing the functions of E1 and E4 either stably integrated in the genome or having one of the functions provided with a helper virus; see Falck-Pedersen, col. 9, lines 29-41) to produce $E1^{-}$ $E4^{-}$ adenovirus vectors as the necessary E4 function is provided in *trans*. In view of the teachings of Lusky, one would not be motivated to provide E4 ORF6 function in *cis*. Instead, one would have been motivated to create replication-defective adenovirus vectors with minimal E4 regions and strongly consider supplying at least E4 ORF6 in *trans*.

Applicants note that it is unclear how the teachings of Mehtali and Falck-Pedersen should be combined to obtain "optimal results". Falck-Pedersen discloses that the viral yield of an E1-deficient Ad7a virus on 293/ORF6 cells (which provide ORF6 in *trans*) was essentially the same as that expected for Ad5 infections. See Falck-Pedersen, Example 6 (col. 14, line 20 to col. 15, line 2). One would never expect propagation of a non-group C adenovirus in an Ad5 complementing cell line to be better than propagation of Ad5. Thus, there is no motivation to combine Mehtali and Falck-Pedersen to achieve "optimal" propagation of replication deficient adenoviruses.

Applicants further submit that there is no reasonable expectation of success for the invention, as reflected in the amended claims. The claims, as amended, require the propagation of a replication-defective adenovirus from subgroup D. Mehtali does not provide any examples of using alternative serotypes, while Falck-Pedersen only exemplifies propagation of Ad7a (subgroup B). There are sufficient sequence differences in the E4 regions of adenoviruses of subgroups B, C, and D (see reference **C02**, page 456, lines 6-10), that it would be unpredictable whether genetic manipulation in the E4 region of a subgroup D adenovirus would result in a viable adenovirus. Similar results were seen when the E1B region of subgroup B adenoviruses was genetically manipulated. See reference **C01**, abstract. A critical pIX promoter, only present in subgroup B adenoviruses, was inadvertently deleted resulting in vector instability. See id. While the Ad35 genome could be manipulated to retain the pIX promoter and provide vector stability, it was unclear at the time of the present invention whether a critical function was present in the E4 region of subgroup D adenoviruses. Such a critical function could prevent the development of $E4^-$ adenoviruses from subgroup D. Therefore, Falck-Pedersen's disclosure of a replication-defective Ad7a adenovirus with an intact E4 region does not provide a reasonable expectation of success for an $E4^-$ replication-defective adenovirus of subgroup D.

Claims 1-11, 21-23 and 84 were rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Falck-Pedersen, Li and Mehtali, and further in view of Megede (Megede *et al.*, 2000, J. Virol. 74:2628-2635). Applicants respectfully traverse.

Falck-Pedersen, Li and Mehtali have been discussed above and do not teach the HIV-1 gag antigen as a gene of interest. Megede teaches that gag is an important target for host cell-mediated immune control of HIV. See Megede, abstract. Megede does not provide any teachings with respect to adenovirus or its propagation.

The Examiner contends that the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made because (1) one would have been motivated to use HIV-1 gag as the gene of interest in order to express gag proteins for vaccines; and (2) there would have been a reasonable expectation of success given that the HIV-1 gag gene has been characterized and the underlying techniques are widely known and commonly used.

As Megede fails to remedy the deficiencies of Mehtali, Falck-Pedersen and Li, with respect to independent claim 1, Applicants respectfully submit that the present invention is not obvious in view of Mehtali, Falck-Pedersen and Li in view of Megede.

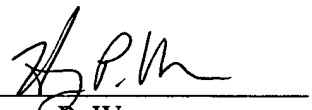
For the above reasons, Applicants respectfully request withdrawal of the rejections under 35 U.S.C. 103.

Should the Examiner maintain one or more of the above rejections, Applicants respectfully request that the Examiner consider all rebuttal arguments and evidence presented by Applicants and provide a clear line of reasoning for any arguments made by the Examiner.

CONCLUSION

Applicants believe the claims are in condition for allowance. An early indication of the same is requested. The Examiner is invited to contact Applicants' Attorney at the telephone number given below, if such would expedite the allowance of this application.

Respectfully submitted,

Date: April 28, 2008 By: 

Henry P. Wu
Reg. No. 44,412
Attorney for Applicants

Merck & Co., Inc.
P.O. Box 2000
Rahway, NJ 07065-0907
732.594.5312